

**Section II (Remarks)****A. Summary of Amendment to the Claims**

By the present Amendment, claims 1-6, 15, 17 and 18 have been amended. Claims 9-11 remain withdrawn. No new matter within the meaning of 35 U.S.C. §132(a) has been introduced by the foregoing amendments.

The amendments made herein are fully consistent with and supported by the originally-filed disclosure of this application. Specifically, support for the amendment to claims 1-6, 15, 17 and 18 is found at page 6, lines 7-8, which states, “[e]xemplary rifamycins are rifalazil (3’-hydroxy-5’-(4-isobutyl-1-piperazinyl) benzoxazinorifamycin; also known as KRM-1648)...” and at page 7, line 6, which states “[r]ifamycins include rifalazil,...”

**B. Rejection of Claims 20-21 for Double Patenting**

In the August 10, 2007 Office Action, claims 20, 21 are provisionally rejected on the ground of non-statutory obviousness type double patenting over claim 1 of co-pending application No. 10/651,865. Application No. 10/651,865 is currently abandoned, but is also being revived for the purpose of filing a continuation application with claims directed to unclaimed subject matter.

Applicant respectfully requests to hold this issue in abeyance until such time as patentable subject matter is achieved in either the current application or co-pending application No. 10/651,865.

**C. Rejection of Claims 1-8, 12-16 under 35 U.S.C. § 112**

Claims 1-8 and 12-16 were rejected under 35 U.S.C. § 112, first paragraph on the basis that the specification purportedly does not provide enablement for preventing atherosclerosis in a patient by administering a rifamycin. Applicant respectfully traverses the rejection if applied to the amended claims.

The Office Action stated that Applicant's disclosure "fails to provide information sufficient to practice the invention," and that the guidance of the specification "is completely lacking" towards the treating and prevention of atherosclerosis associated disease. (Office Action, pg. 5, ll. 12-13; pg. 4, ln. 23) However, the specification clearly teaches that one of skill in the art can look for a reduction in C-reactive protein as an indication of the success of treatment and prevention for atherosclerosis.

"An atherosclerosis-associated disease has been treated or prevented when one or more tests of the disease (e.g., any of those described above) indicate that the patient's condition has improved or the patient's risk reduced. In one example, a **reduction in C-reactive protein to normal levels indicates that an atherosclerosis associated disease has been treated or prevented.**" (emphasis added) (Present Application, pg. 5, ll. 20-24)

Recognized medical journals have supported the use of C-reactive protein levels as a measure of the success of atherosclerosis treatment. For example, two abstracts are included in Exhibit A, namely "Correlations of high-sensitivity C-reactive protein and atherosclerosis in Japanese type 2 diabetic patients," by Anan et al., (European Journal of Endocrinology, 2007 Sep.; 157(3):311-317; also available at [www.ncbi.nlm.nih.gov/pubmed/17766713](http://www.ncbi.nlm.nih.gov/pubmed/17766713)) and "C-reactive protein levels do not correlate with retinal artery occlusion but with atherosclerosis," by Goldenberg-Cohen et al., (Eye, 2008, Jun. 6; also available at [www.ncbi.nlm.nih.gov/pubmed/18535598](http://www.ncbi.nlm.nih.gov/pubmed/18535598)). These abstracts teach measuring C-reactive protein levels to determine whether atherosclerosis has been treated.

Thus, there is disclosure in the specification for testing whether a patient's atherosclerosis has improved or been prevented that is well known by those of skill in the art. However, in the interest of facilitating allowance, Applicant has amended claim 1 to recite:

"A method of **treating** an atherosclerosis-associated disease in a patient in need thereof, said method comprising administering to said patient rifalazil in an amount effective to treat said atherosclerosis-associated disease in

disease in said patient.” (emphasis added)

Since the specification provides sufficient support to enable one of skill in the art, namely a physician, to measure the reduction in the C-reactive protein level of a patient as a measure of successful *treatment* of atherosclerosis-associated disease in a patient following the administration of rifalazil, the specification provides enablement for amended claim 1 and those claims dependent therefrom. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

**D. Rejection of Claims 1-8, 12-21 under 35 U.S.C. § 102(e) to U.S. Publication No. 2004/0014749**

In the August 10, 2007 Office Action, claims 1-8, 12-21 were also rejected under 35 U.S.C. 102(e) as purportedly being anticipated by Michaelis et al. (U.S. Publication No. 2004/0014749; hereinafter “‘749 publication”). Applicants respectfully traverse.

Independent Claims 1, 17, and 20

Independent Claims 1, 17, and 20, as amended herein, recite:

1. “A method of treating an atherosclerosis-associated disease in a patient in need thereof, said method comprising **administering to said patient rifalazil** in an amount effective to treat said atherosclerosis-associated disease in said patient.”

17. “A method of reducing the level of C-reactive protein in a patient identified as having increased levels of C-reactive protein, said method comprising **administering to said patient rifalazil** in an amount sufficient to reduce the level of C-reactive protein.”

20. “A method for reducing Chlamydia pneumoniae replication in macrophages or foam cells in a patient in need thereof, said method comprising **administering rifalazil** to said patient in an amount effective to reduce Chlamydia pneumoniae replication in macrophages or foam cells in said patient.” (emphasis added)

The ‘749 Publication

The ‘749 publication discloses sulfhydryl rifamycin compositions and methods for treating diseases using these compositions. (See Abstract, ‘749 publication) The ‘749 publication does not disclose or teach the administration of rifalazil to a patient for the treatment of atherosclerosis or any other condition.

#### Analysis

The ‘749 Publication teaches sulfhydryl compounds, but does not teach or suggest compounds that do not include a sulfhydryl group (such as rifalazil, the specific rifamycin analog used in the currently amended claims). Accordingly, the sulfhydryl group is relevant to the compound’s utility.

Therefore, the ‘749 Publication does not disclose the claimed subject matter, and it would not be obvious to modify the teachings of the ‘749 publication to arrive at the claimed subject matter.

#### **E. Rejection of Claims 1-8, 12-21 under 35 U.S.C. § 102(e) to U.S. Publication No. 2004/0014750**

In the August 10, 2007 Office Action, claims 1-8, 12-21 were also rejected under 35 U.S.C. 102(e) as purportedly being anticipated by Michaelis et al. (U.S. Publication No. 2004/0014750; hereinafter “‘750 publication”). Applicants respectfully traverse.

#### Independent Claims 1, 17, and 20

Independent Claims 1, 17, and 20, as amended herein, recite:

1. “A method of treating an atherosclerosis-associated disease in a patient in need thereof, said method comprising **administering to said patient rifalazil** in an amount effective to treat said atherosclerosis-associated disease in said patient.”

17. “A method of reducing the level of C-reactive protein in a patient identified as having increased levels of C-reactive protein, said method comprising **administering to said patient rifalazil** in an amount sufficient to reduce the level of C-reactive protein.”

20. “A method for reducing *Chlamydia pneumoniae* replication in macrophages or foam cells in a patient in need thereof, said method comprising **administering rifalazil** to said patient in an amount effective to reduce *Chlamydia pneumoniae* replication in macrophages or foam cells in said patient.” (emphasis added)

#### The ‘750 Publication

The ‘750 Publication is directed to treating various disorders with metal complexes of rifamycins, not free rifamycins. Because the complexes are formed from the free rifamycins, there would be no motivation to de-complex the complexed rifamycins to arrive at a free rifamycin, and use the free rifamycin for a method of medical treatment. Accordingly, Michaelis does not teach or suggest the claimed subject matter.

#### **F. Rejection of Claim 20 under 35 U.S.C. § 102 (e)**

Claim 20 was rejected under 35 U.S.C. 102(e) as purportedly being anticipated by Mitchell et al. (U.S. Patent No. 6,562,582; hereinafter “Mitchell”). Applicants respectfully traverse.

Claim 20 was provided above.

Mitchell was cited as disclosing that rifamycins can inhibit and possibly kill members of the Chlamydial species, including *C. pneumoniae*, but does not disclose or teach rifalazil. However, Mitchell states that:

the inventors have found that the complete eradication of *Chlamydia* cannot be achieved by the use of any one of these agents alone because none are efficacious against all forms of the Chlamydial life cycle and appear to induce a stringent response in *Chlamydia* causing the replicating phase to transform into the non-replicating phase.

(Mitchell, col. 9, ll. 29-38)

### Analysis

Applicants discovered that rifalazil has efficacy against both the multiplying *and non-multiplying form* of Chlamydia spp., which was neither disclosed nor suggested by Mitchell. Accordingly, Mitchell does not teach or suggest, but rather, teaches away from, the instantly claimed subject matter.

### **G. Rejection of Claim 1 under 35 U.S.C. § 102 (b)**

Claim 1 was rejected under 35 U.S.C. 102(b) as purportedly being anticipated by Kump et al. (U.S. Patent No. 5,147,870; hereinafter “Kump”). Applicants respectfully traverse.

Claim 1 was provided above.

Kump discloses substituted azacyclohexyl derivatives of rifamycins with LDL lowering activity in rats (Kump, Abstract and col. 2, ll. 13-16), but does not teach treating atherosclerosis in animals or humans with rifalazil.

Each of Kump’s azacyclohexyl derivatives included an aromatic ring attached to a piperidine ring, which aromatic ring is not present in rifalazil. This ring is apparently critical to the ability of the derivatives to function for their intended purpose. Accordingly, not only does Kump not disclose the invention as claimed, there would be no motivation to modify Kump to arrive at the claimed invention.

### **H. Rejection of Claim 1 under 35 U.S.C. § 102 (b)**

Claims 17-19 were rejected under 35 U.S.C. 102(b) as purportedly being anticipated by Cox et al. (Annals of Rheumatic Diseases, 1992, 51, 23-34; hereinafter “Cox”). Applicants respectfully traverse.

The subject matter of Claim 17 is discussed above.

Cox teaches treating rheumatoid arthritis with rifampicin (Cox, Abstract), but does not disclose or suggest treating rheumatoid arthritis with rifalazil.

In the instantly claimed invention, by lowering the amount of bacteria in the heart, inflammation in the heart tissue is reduced. This reduction in inflammation results in a lowering of C-reactive protein. Accordingly, though applicants do not claim treating

rheumatoid arthritis, they do claim an overall reduction in C-reactive protein, as a result of treating the (bacterial) cause, rather than the symptom, of the inflammation.

#### Dependent Claims

For all of the above reasons, none of the ‘749 publication, the ‘750 Publication, Mitchell, Kump or Cox discloses or teaches administering rifalazil (namely 3’-hydroxy-5’-(4-isobutyl-1-piperazinyl) benzoxazinorifamycin), to treat atherosclerosis, reduce the level of C-reactive protein, or reduce Chlamydia pneumoniae replication in macrophages or foam cells. As such, none of these references discloses each and every element that is recited by amended independent claims 1, 17, and 20.

Claims 2-8 depend from amended claim 1, and claims 18 and 19 depend from amended claim 17. Since dependent claims are construed to incorporate all of the limitations of the independent claims from which they depend, none of the cited references disclose each and every element of claims 2-8 and claims 18 and 19.

Accordingly, independent claim 1 and dependent claims 2-8 and 12-16 are not anticipated by the ‘749 Publication, the ‘750 Publication, Mitchell, Kump or Cox. Additionally, independent claims 17, dependent claims 18-19, and independent claims 20-21 are also not anticipated by the ‘749 publication, Mitchell, Kump or Cox. As such, Applicant respectfully requests that these rejections be withdrawn.

#### **I. Rejection of Claims 1-8, 12-21 under 35 U.S.C. § 103**

Claims 1-8, 12-16 and 21 are rejected under 35 U.S.C. § 103 as purportedly unpatentable over Baumgart et al (WO 00/01378; hereinafter “Baumgart”) in view of Ullah et al. (U.S. Patent No. 6,235,311; hereinafter “Ullah”). Applicant disagrees and traverses such rejection for the following reasons.

#### Baumgart

Baumgart purportedly teaches methods and pharmaceutical compositions for treating conditions and vascular diseases associated with Chlamydia pneumoniae

infections by administering an effective amount of at least two different antibiotics, including rifamycins. (Baumgart, Abstract)

Baumgart further discloses that the “[e]xamples of the rifamycin claim of antimicrobial agents suitable for use in the methods and pharmaceutical compositions of the present invention include rifampicin, rifabutin, and rifapentin.” (Baumgart, pg. 8, ll. 33-35)

### Ullah

Ullah discloses a pharmaceutical composition that combines aspirin and a statin cholesterol lowering agent “in a manner to minimize the interaction of the aspirin with the statin.” (Ullah, col. 1, ll. 7-11)

### Analysis

As stated above, independent claims 1, 17, 20 and 21 have been amended to recite the administration of rifalazil, specifically, for the treatment of atherosclerosis in claim 1, to reduce the level of C-reactive protein in claim 17, or to reduce Chlamydia pneumoniae replication in macrophages or foam cells in claims 20 and 21.

Neither Baumgart nor Ullah discloses or suggests administering rifalazil in any form. While Baumgart specifically states that “rifampicin, rifabutin, and rifapentin” are suitable for use, he does not name rifalazil. (Baumgart, pg. 8, ll. 33-35)

Thus, not all of the claim limitations in independent claims 1, 17, 20 and 21 are disclosed or suggested by Baumgart in view of Ullah.

Since dependent claims are construed to incorporate all of the limitations of the independent claims from which they depend, none of the cited references disclose each and every element of claims 2-8 and claims 18 and 19 as well. As such, claims 1-8 and 12-21 are patentably distinguished over Baumgart in view of Ullah. Applicant respectfully requests withdrawal of these rejections.

**J. Rejection of Claims 1-5, 7, 8, 12-15 and 21 under 35 U.S.C. § 103**

Claims 1-5, 7, 8, 12-15, 21 are rejected under 35 U.S.C. § 103 as purportedly unpatentable over Yamashita et al. (EP 0778022; hereinafter “Yamashita”) in view of Baumgart in view of Ullah. Applicant respectfully traverses the rejection.

As acknowledged by the Examiner, Yamashita discloses treating diseases resulting from Chlamydia infection, including coronary disease, by administering rifamycin derivatives. However, Yamashita does not teach or suggest treating atherosclerosis by administering rifamycin. (Office Action, pg. 14, ll. 1-2)

As stated above, Baumgart teaches methods and pharmaceutical compositions for treating conditions and vascular diseases associated with *Chlamydia pneumoniae* infections by administering an effective amount of at least two different antibiotics, including certain rifamycins. (Baumgart, Abstract) Baumgart further teaches that the purpose of administering two different antibiotics is that “in the case of ‘difficult to eradicate’ intracellular pathogens, widespread use of a single antibiotic regimes has serious potential adverse consequences for the population at large as well as the individuals who may develop resistant infections.” (Baumgart, pg. 2, ll. 4-7) Additionally, Baumgart also teaches that “widespread use of single antibiotic regimes may result in greater resistance among *C. pneumoniae* and other important human pathogens than those being treated.” (Baumgart, pg. 2, ll. 15-17)

Baumgart clearly teaches away from treating bacterial infections with single antibiotic regimes. Since Baumgart also clearly states that using antibiotics in this manner may result in greater resistance for pathogens other than those being treated, one of skill in the art would not be motivated to combine the teachings of Baumgart with those of Yamashita, to administer rifamycin, or for that matter rifalazil, to treat atherosclerosis (Claim 1), or to treat *Chlamydia pneumoniae* infection in macrophages or foam cells (Claim 21).

Additionally, one of skill in the art would also not be motivated to combine Ullah with either Yamashita or Baumgart, because Ullah teaches a pharmaceutical composition that is a combination of aspirin and a statin cholesterol lowering agent combined together “in a manner to minimize the interaction of the aspirin with the statin.” (Ullah, col. 1, ll.

7-11) Ullah further teaches that the statin and aspirin must be combined in a careful manner “to insure that drug interaction, including physical and chemical incompatibility, and side effects, are kept to a minimum...” (Ullah, col. 1, ll. 22-25)

One of skill in the art would not have a reasonable expectation that the statin and aspirin could further be combined with rifalazil in a manner in which possible drug interactions, physical and chemical incompatibilities, and side effects are all avoided. .

Accordingly, one of skill in the art would not be motivated to combine the teaching of Yamashita with that of Baumgart and/or Ullah. Accordingly, independent claims 1 and 21, and dependent claims 2-5, 7, 8, and 12-15 are patentably distinguished over Yamashita in view of Baumgart and further in view of Ullah. As such, Applicant respectfully requests that this rejection be withdrawn.

### **CONCLUSION**

Based on the foregoing, all of Applicants’ pending claims 1-8 and 12-21 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a Notice of Allowance. If any issues require further resolution, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

/david bradin/

David Bradin

Reg. No. 37,783

Attorney for Applicants

INTELLECTUAL PROPERTY/  
TECHNOLOGY LAW  
Phone: (919) 419-9350  
Fax: (919) 419-9354  
Attorney File No.: 4354-112

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